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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

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04/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,843	PELED ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *401,411,414,416,419,422-424,464,465,469-471 and 478-480* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401, 411, 414, 416, 419, 422-424, 464, 465, 469-470, 471 and 478-480* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/04/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Toni Peled filed on 02-22-2010 ("2010 Peled Decl.").
3. Claims 401, 411, 414, 416, 419, 422-424, 464, 465, 469-470, 471 and 478-480 are pending. Claims 437 and 438 have been canceled and claims 401 and 411 have been amended by Applicants' amendment filed on 02-22-2010.
4. Therefore, claims 401, 411, 414, 416, 419, 422-424, 464, 465, 469-471 and 478-480 are currently under examination to which the following grounds of rejection are applicable.

Priority

This application which claims the benefit under 35 U.S.C. 119(e) of prior-filed provisional application 60/404,137, filing date 08/19/2002, and 60/376,183, filing date 04/30/2002, is acknowledged.

Review of the priority documents provides no literal or figurative support for the claimed invention of "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide". Therefore, the priority date for the claimed limitation "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide" is found in the disclosure of the instant U.S. Application filed on 02-09-2004.

Withdrawn rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 101

In view of Applicants' amendment of claim 411 in Applicants' response filed on 01-21-2010 to introduce the limitation "isolated" rejection of claim 411 and dependent claims 465 and 478-480 under 35 U.S.C. § 101 has been withdrawn.

35 USC § 112- First paragraph- Written description

In view of Applicants' amendment of claims 401, 411, 464, 465, 469, 470, 471, and 478-480 and cancelation of claims 437 and 438 in Applicants' response filed on 01-21-2010, rejection of claims 401 and dependent claims 414, 416, 419, 422-424, 437, 438, 464 and 469-471 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn.

Claim Rejections - 35 USC § 103

In view of Applicants' cancelation of claims 437 and 438 in Applicants' response filed on 01-21-2010, rejection of claims 437 and 438 under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002) and Banasik et al., (1992, JBC, pp. 1569-1575, of record) is rendered moot.

Rejections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103

Claims 401 and 411 have been amended to recite "a combination of cytokines including stem cell factor, thrombopoietin, FLt3 ligand, IL-6 and optionally IL-3". Thus the phrase "a combination of cytokines including stem cell factor, thrombopoietin, FLt3 ligand, IL-6 and

optionally IL-3" can be broadly but reasonably interpreted as including any combination of the cited cytokines. Thus a combination of stem cell factor, thrombopoietin (TPO) and interleukin-1 (IL-I) will fall within the scope of claims 401 and 411. Additionally, claims 411 and dependent claims 465 and 478-480 are product-by-process claims. All what is required in the claimed invention of claim 411 is the structure implied by the process of making. Accordingly, all what is required by the claimed population of isolated transplantable hematopoietic cells is a population of CD34+ hematopoietic stems cells with a greater percentage of CD34+/CD38- and CD34+/lin- cells. Product-by-process limitations are considered only in as far as the method of production imparts distinct structural or chemical characteristics or properties to the product. Therefore if the product, as claimed, is the same or obvious over a product of the prior art (*i.e.* is not structurally or chemically distinct), the claim is considered unpatentable over the prior art, even though the prior art product is made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

Claims 401, 411, 414, 416, 419, 422-424, 464, 465, 469-470, 471 and 478-480 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002).

Response to Applicants' Arguments as they apply to rejection of claim 401, 411, 414, 416, 419, 422-424, 464, 465, 469-471 and 478-480 under 35 USC § 103

At page 6 of the remarks filed on 02-22-2010, Applicants essentially argue that: 1) the combination of Brown and Block teaches away from the instant invention, particularly because

Brown discloses preferentially culture conditions for hematopoietic ES cells expansion free of serum, 2) Brown does not teach or suggest to the skilled artisan that the claimed nicotinamide concentrations of 1.0 mM to 10 mM in serum free media maintains CD34+ hematopoietic cells in an undifferentiated state and enriches for CD34+/CD38- and CD34+/lin- cells in a serum containing culture medium, 3) Block essentially discloses that nicotinamide was used in the culture/expansion to maintain differentiated hepatocytes (see Block, col. 8, lines 26-28), 4) hepatocytes are a completely different cell population that the claimed CD34+ hematopoietic stem cell population, 5) Block culture medium does not teach any of the cytokines recited in the instant claims, 6) the entire focus of Block is to provide a chemically defined culture medium that is serum free (col. 1, lines 43-50; col. 4, lines 8-10), and 7) the 2010 Peled Decl. and 2008 Peled Decl. shows how using nicotinamide in the range of 1.0 mM to 10 mM inhibits differentiation of CD34+ hematopoietic cells as evidenced by the unexpectedly substantially increased cell density of CD34+/CD38- and CD34+/lin- cells while permitting expansion, *ex vivo*. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), 2) and 5), in response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is relevant to point that the ultimate goal of expanding CD34+, CD34+/CD38- and CD34+/lin- cells hematopoietic stem cells is to provide long term expansion of stem cells. Note that the claimed invention does not place any limitation on how long the population of CD34+ hematopoietic cells is cultured for expansion in the presence of exogenously added nicotinamide.

As previously indicated, regarding *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from umbilical cord blood, Brown R. discloses the presence of appropriate growth factors in the culture medium for expansion CD34+stem cells such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population. Additionally, the basal medium of Brown for expansion of CD34+/CD38- cells *ex vivo* includes nicotinamide at concentration of 4 mg/L (4 mg/L is equivalent to 0.033mM) which can be optimized to concentrations of 40 mg/L (e.g., equivalent to 0.330mM). In contrast to Applicants' contention, Brown R. explicitly exemplifies cultures of bone marrow CD34+ enriched populations showing CD34+/CD38- cells with significant expansion at days 3, 7 and 14, in the absence and presence of serum, albeit maximal output of CD34+/CD38- cells were observed at days 3 and 7 and a higher total clonogenic potential was observed in the serum-free cultures (¶ [0121] of the published application). Fig. 2 of Brown illustrates fold increases in the amount of CD34+ in both serum-containing and serum-free medium.

Regarding 3) and 4), as stated previously, Block clearly teaches that various growth factors can be added to the stock basal media to induce accelerated growth (col. 11, lines 28-38) including concentrations of nicotinamide in the range of 1-3050 mg/L, preferably 610.0 mg/L (610-3050 mg/L is equivalent to 5 to 25 mM of nicotinamide), (see Table II; col. 10, lines 30-50). Furthermore, Block teaches that after 14 days of growth, removal of nicotinamide from media components has the most dramatic effect in reducing cell proliferation, only second to removal of Dexamethasone. Thus, Block unequivocally teaches that nicotinamide is an essential component in a basal media inducing DNA replication. It is noted that Block et al. in preferred

embodiments discloses proliferation and long-term expansion of hepatocytes. However, Block discloses that hepatocytes proliferate directly or via facultative stem cell growth. Thus proliferation of mature adult hepatocytes taught by Block implicitly includes proliferation of "oval cells," which mature into hepatocytes ((¶ [7] of the published application). If DNA synthesis significantly decreases in proliferating hepatocytes cultures derived from stem cells maintained in the absence of Nicotinamide in relation to cultures maintained in the presence of Nicotinamide at 610.0 mg/L (e.g., 5mM), removal of Nicotinamide should be reasonably expected to inhibit CD34+ hematopoietic stem cell proliferation for the same reason it prevents or reduces proliferation of hepatocytes derived from stem cells -both hepatocyte stem cell and CD34+ hematopoietic stem cell require DNA proliferation for *ex vivo* expansion. Applicants have not provided probative evidence to the contrary. In contrast to Applicants' statements, hematopoietic stem cell and hepatocytes stem cells have functions and phenotypes both different and identical. Hepatocytes proliferation directly or via facultative stem cell growth leads to appearance of bile duct-like structures (Block, Fig 6D, for example) whereas proliferation of hematopoietic stem cells does not. However, both hepatocyte stem cells and CD34+ hematopoietic stem cells require DNA synthesis for long-term expansion/ proliferation, *ex vivo*.

Regarding 6), Block discloses at col. 1, lines 43-50 a chemically defined culture medium for long-term expansion free of animal serum (col. 1. line 50). The specification as filed does not provide a closed definition of the term "serum" but teaches some examples, e.g., serum thymic factor, 1% bovine serum albumin, 0.5% bovine serum albumin. As such, and in view of the customary and ordinary meaning of the term "serum" in the art as "the watery portion of an animal fluid remaining after coagulation" (Webster's Seventh New Collegiate Dictionary, G. C.

Merriam Co.), the term serum is embraced by components of the chemically defined culture medium taught by Block such as albumin, glucose and others (col. 8, lines 1-5, for example)

Regarding 7), the 2008 Peled decl. was addressed in detail in the office action filed 03-30-209. The 2010 Peled decl. merely indicates that Fig. 1 discloses hematopoietic CD34+ cell cultures initiated in the presence of the four claimed cytokines: SCF, TPO, FLt3, IL-6 at concentration of 50ng/m each, with or without different concentrations of nicotinamide within the claimed range of 1.0 to 10.0 mM. In contrast to Applicants' arguments, it is unclear how the "unexpectedly substantially increased cell density of CD34+/CD38- and CD34+/lin- cells while permitting expansion, *ex vivo"* are determined in the 2010 Peled decl. FIG. 1 of the 2010 Peled decl. illustrates that cells cultures supplemented with various concentrations of 1 to 20 mM nicotinamide for 7, 14 and 21 days resulted in increased CD34+/CD38- cells density at days 7, 14 and 21 for cultures supplemented with 5 to and 20 mM nicotinamide, as compared with the untreated (cytokines only) control. Note that Fig. 1 displays CD45+/CD34+cells density and not CD34+/CD38- cells density. The examiner assumes based on the 2010 Peled decl. statement that this a typographical error. Fig. 2 illustrates that CD34+/CD38- cells density at days 7, 14 and 21 is not enhanced by the addition of 5 mM nicotinamide, as compared with the untreated (all five cytokines) control. There is not evidence of any statistical analyses being performed, much less unexpectedly substantially increased cell density of CD34+/CD38- and CD34+/lin- cells, at the most there is an increase in CD34+/CD38- cells density after 7, 14 and 21 days incubation period at concentrations of 10 to 20 mM nicotinamide as compared with the untreated control as illustrated in Fig. 1.

Accordingly, in view of the teachings of Brown and Block, it would have been obvious for one of ordinary skill in the art that the method of expanding CD34+ cells was recognized as part of ordinary capability of one of skill in the art. One of skill in the art would have been capable of applying this known technique of expanding of CD34+ hematopoietic stem cells, total number of cell and clonability by using the known method of culturing CD34+ cells as in Brown. Furthermore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, to increase the concentration of exogenously added nicotinamide to the culture media taught by Brown in an attempt to provide an improved formulation of the culture medium for preferential *ex vivo* expansion (e.g. proliferation) of CD34+ hematopoietic stem cells, particularly because Block clearly discloses, in an unequivocal manner, that exposing a mixed population of hepatocytes including stem cells to nicotinamide at concentrations of 0-3050 mg/L, and preferentially 610.0 mg/L (e.g., equivalent to 5 mM), sustained long term proliferation and viability of hepatocytes. Hence Applicant has presented insufficient evidence commensurate with the scope of the claims, to rebut the combination of Brown and Block rendering obvious the instant claims with respect to expanding a population of CD34+ hematopoietic stem cells, *ex vivo*, comprising culturing said population with any combination of the claimed cytokines while simultaneously providing in the same culture medium concentrations of 1mM to 10mM of nicotinamide.

References made of record in a PTO-892 Form to complete the record

Schwartz et al., 2002,*J. Clin. Invest.* pp. 1291-1302 .

Conclusion

Claims 401, 411, 414, 416, 419, 422-424, 464, 465, 469-470, 471 and 478-480 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633